U.S. DEPARTMENT OF COMMERCE
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10-597

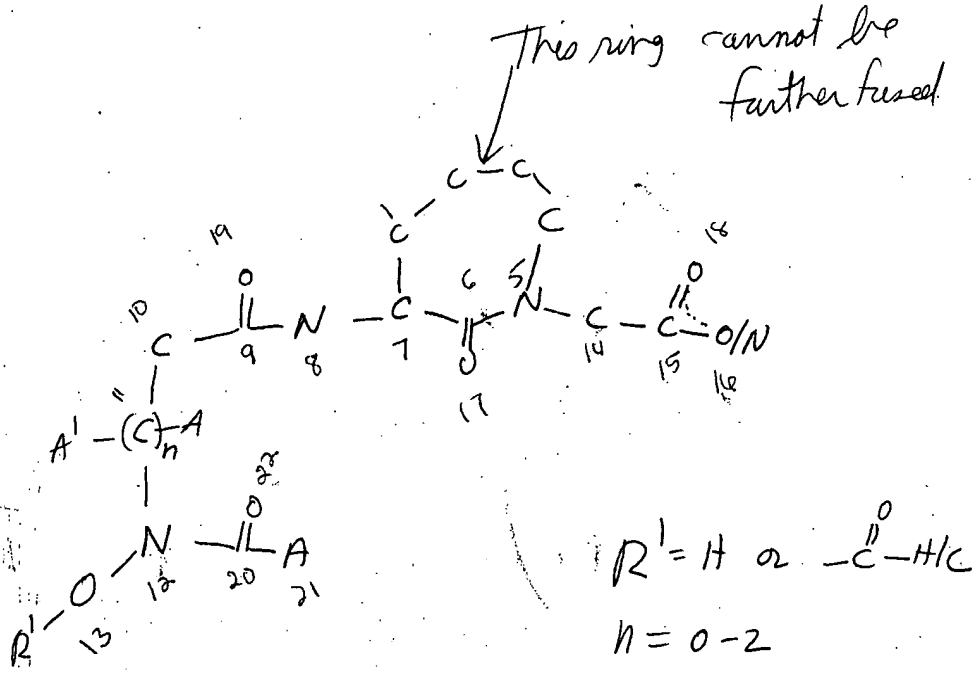
SEARCH REQUEST FORM

Requestor's Name: Bond Serial Number: 833172

Date: 10/23 Phone: 4718 Art Unit: 1202

Search Topic:

Please write a detailed statement of search topic. Describe specifically as possible the subject matter to be searched. Define any terms that may have a special meaning. Give examples or relevant citations, authors keywords, etc., if known. For sequences, please attach a copy of the sequence. You may include a copy of the broadest and/or most relevant claim(s).



R^1 = H or $-\overset{O}{\overset{\|}{C}}-H/C$

$n = 0-2$

$A = H/CH_3$

STAFF USE ONLY

10/25

Date completed: 10/23

Searcher: Mary 4218

Terminal time: 16

Elapsed time: _____

CPU time: _____

Total time: _____

Number of Searches: _____

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Search Site

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Type of Search

_____ N.A. Sequence

_____ A.A. Sequence

_____ Structure

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✓ IG Suite

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_____ Dialog

_____ APS

_____ Geninfo

_____ SDC

_____ DARC/Questel

_____ Other

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FILE 'REGISTRY' ENTERED AT 11:11:03 ON 23 OCT 1997
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STRUCTURE FILE UPDATES: 19 OCT 97 HIGHEST RN 195701-91-8
DICTIONARY FILE UPDATES: 22 OCT 97 HIGHEST RN 195600-69-2

Searched By: Mary Hale 308-4258

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Please note that search-term pricing does apply when conducting SmartSELECT searches.

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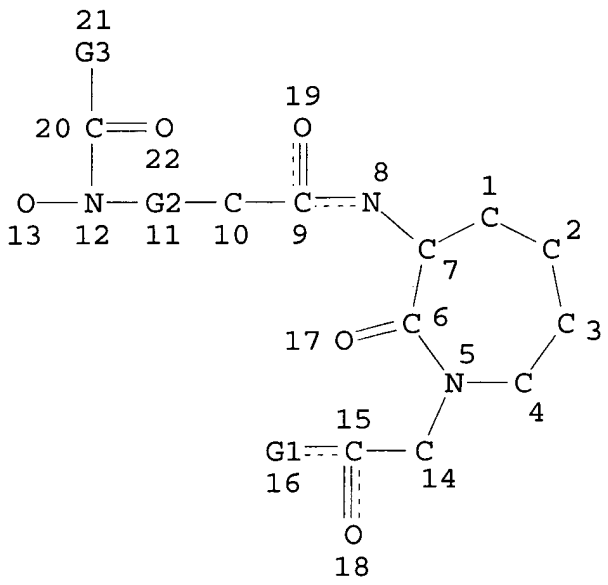
L1 STR



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VAR G3=H/ME
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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
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NUMBER OF NODES IS 22

STEREO ATTRIBUTES: NONE
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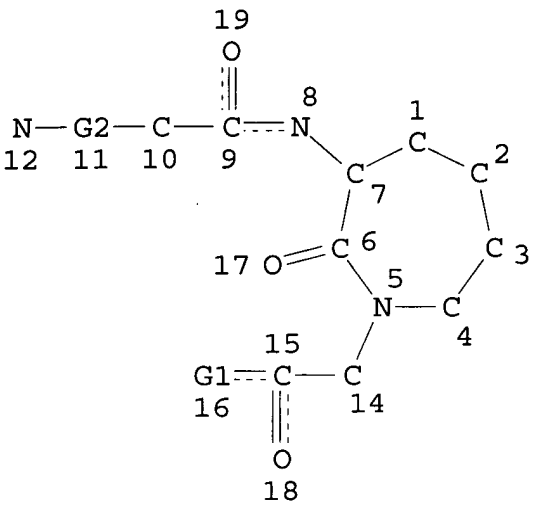
Searched By: Mary Hale 308-4258

=> d l6 que stat;d 1-11 ide cbib abs
L4 STR



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NUMBER OF NODES IS 18

STEREO ATTRIBUTES: NONE
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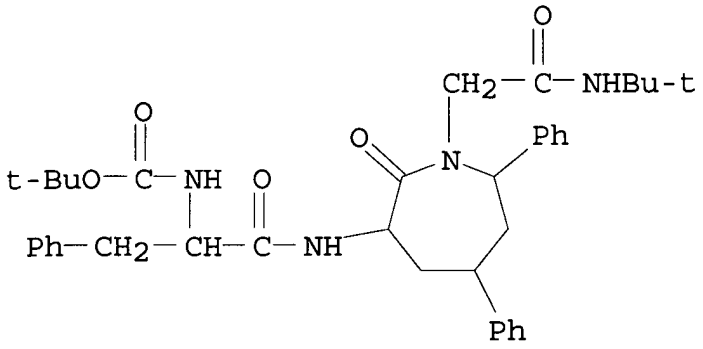
SEARCH TIME: 00.00.03

L6 ANSWER 1 OF 11 REGISTRY COPYRIGHT 1997 ACS
RN 175969-92-3 REGISTRY
CN Carbamic acid, [2-[[1-[2-[(1,1-dimethylethyl)amino]-2-oxoethyl]hexahydro-2-oxo-5,7-diphenyl-1H-azepin-3-yl]amino]-2-oxo-1-(phenylmethyl)ethyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C38 H48 N4 O5
SR CA

LC STN Files: CA, CAPLUS



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 124:317009 Substituted (phenylureido)hexahydroazepinones and -tetrahydrobenzazepinones as selective CCK-B receptor antagonists useful in the treatment and prevention of gastrointestinal disorders, pain and anxiety disorders. Lowe, John A., III (Pfizer Inc., USA). U.S. US 5484917 A 960116, 47 pp. Cont.-in-part of U.S. Ser. No. 825,677, abandoned. (English). CODEN: USXXAM. APPLICATION: US 93-78125 930616. PRIORITY: US 92-825677 920127.

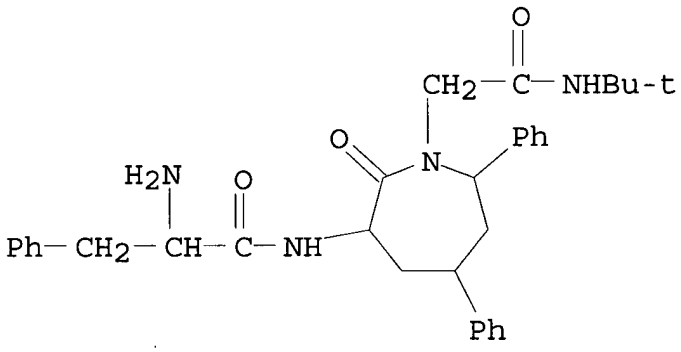
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The present invention relates to novel substituted hexahydroazepinones and tetrahydrobenzazepinones of the formulas I and II wherein Y1 and Y2 are independently selected from the group consisting of, e.g., Ph, thienyl, pyridyl, furyl, pyrimidyl; W1 and W2 are independently selected from, e.g., halo, nitro, amino; Z1 and Z2 are independently selected from the group consisting of, e.g., halo, (C1-C6) alkyl; R1 is Ph, CO2R2, SO2NR3R6 or CONR4R5, wherein said Ph may optionally be substituted with one or two substituents independently selected from halo, (C1-C6) alkyl, (C1 -C6) alkoxy, nitro, amino and trifluoromethyl, and wherein R2, R3, R4, R5 and R6 are independently selected from hydrogen, (C3-C12) alkyl and fused, satd. carbocyclic systems contg. two or three rings, which are selective CCK-B receptor antagonists useful in the treatment and

prevention of gastrointestinal disorders, pain and anxiety disorders (no data). Thus, e.g., bromination of 5-phenyl-2,3,4,5-tetrahydro-1H-(1)benzazepin-2-one afforded diastereomeric 3-bromides; alkylation with N-tert-butyliodoacetamide [to yield N-tert-butyl-2-[3-bromo-2-oxo-5-phenyl-2,3,4,5-tetrahydro-1H-(1)benzazepin-1-yl]ethanoic acid amide], azidation, hydrogenation (to the amine), and carbamoylation with m-tolyl isocyanate afforded N-tert-butyl-2-[3-(3-(3-tolyl)ureido)-2-oxo-5-phenyl-2,3,4,5-tetrahydro-1H-(1)benzazepin-1-yl]ethanoic acid amide III.

L6 ANSWER 2 OF 11 REGISTRY COPYRIGHT 1997 ACS
RN 152681-71-5 REGISTRY
CN 1H-Azepine-1-acetamide, 3-[(2-amino-1-oxo-3-phenylpropyl)amino]-N-(1,1-dimethylethyl)hexahydro-2-oxo-5,7-diphenyl- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C33 H40 N4 O3
SR CA
LC STN Files: CA, CAPLUS, USPATFULL



2 REFERENCES IN FILE CA (1967 TO DATE)
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GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The present invention relates to novel substituted hexahydroazepinones and tetrahydrobenzazepinones of the formulas I and II wherein Y1 and Y2 are independently selected from the group consisting of, e.g., Ph, thienyl, pyridyl, furyl, pyrimidyl; W1 and W2 are independently selected from, e.g., halo, nitro, amino; Z1 and Z2 are independently selected from the group consisting of, e.g., halo, (C1-C6) alkyl; R1 is Ph, CO2R2, SO2NR3R6 or CONR4R5, wherein said Ph may optionally be substituted with one or two substituents independently selected from halo, (C1-C6) alkyl, (C1 -C6) alkoxy, nitro, amino and trifluoromethyl, and wherein R2, R3, R4, R5 and R6 are independently selected from hydrogen, (C3-C12) alkyl and fused, satd. carbocyclic systems contg. two or three rings, which are selective CCK-B receptor antagonists useful in the treatment and prevention of gastrointestinal disorders, pain and anxiety disorders (no data). Thus, e.g., bromination of 5-phenyl-2,3,4,5-tetrahydro-1H-(1)benzazepin-2-one afforded diastereomeric 3-bromides; alkylation with N-tert-butyliodoacetamide [to yield N-tert-butyl-2-[3-bromo-2-oxo-5-phenyl-2,3,4,5-tetrahydro-1H-(1)benzazepin-1-yl]ethanoic acid amide], azidation, hydrogenation (to the amine), and carbamoylation with m-tolyl isocyanate afforded N-tert-butyl-2-[3-(3-(3-tolyl)ureido)-2-oxo-5-phenyl-2,3,4,5-tetrahydro-1H-(1)benzazepin-1-yl]ethanoic acid amide III.

REFERENCE 2: 120:191557 3-(Phenylureido)azepin-2-ones and -benzazepin-2-ones useful as cholecystokinin receptor antagonists. Lowe, John A., III (Pfizer Inc., USA). PCT Int. Appl. WO 9315059 A1 930805, 133 pp. DESIGNATED STATES: W: AU, BR, CA, DE, FI, HU, JP, KR, NO, PL, RU, US; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 92-US10720 921216. PRIORITY: US 92-825677 920127.

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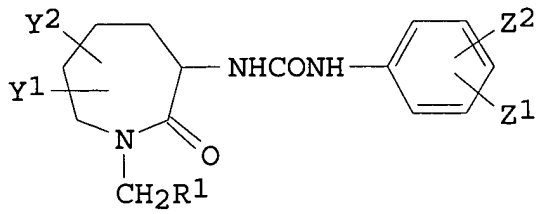

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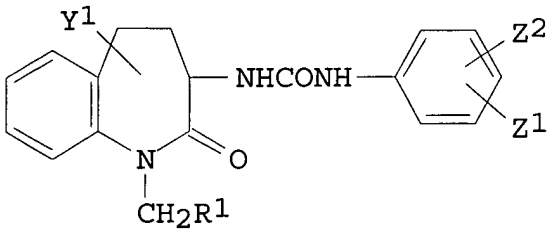
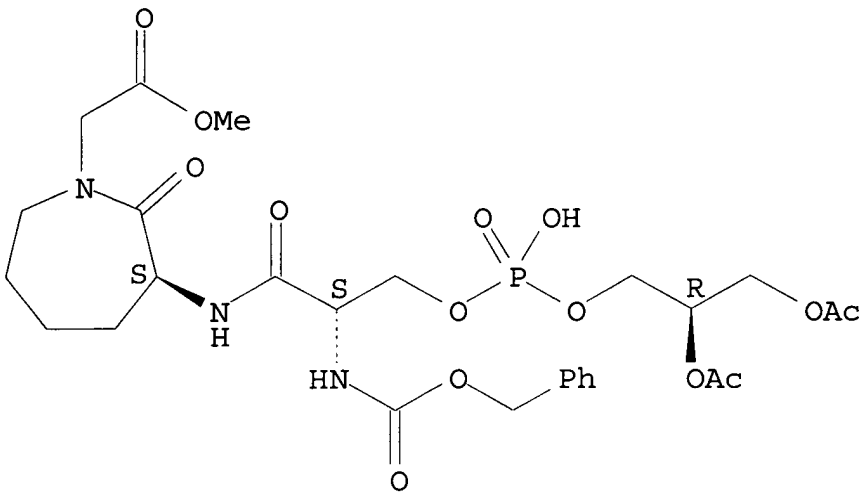


II

AB The title compds. I [R1 = (un)substituted Ph, CO2R2, SO2NR3R6, CONR4R5; R2-R5 = H, C3-12 alkyl, fused and satd. carbocyclic systems contg. 2 or 3 rings; R6 = not defined; Y1, Y2 = (un)substituted Ph, (un)substituted thienyl, (un)substituted pyridyl, (un)substituted furyl, (un)substituted pyrimidyl, C3-8 (un)branched alkyl, C5-8 cycloalkyl; Z1, Z2 = halogen, C1-6 alkyl, C1-6 thioalkyl, C1-6 alkoxy, CF3, C1-6 carboalkoxy, NH2, NO2] and II, useful as cholecystokinin receptor antagonists (no data), are prepd. Thus, N-tert-Bu 2-[3-[3-(3-tolyl)ureido]-2-oxo-5-phenyl-2,3,4,5-tetrahydro-1H-(1)benzazepin-1-yl]ethanoic acid amide (m.p. 263-266.degree.) was prepd. from 5-phenyl-2,3,4,5-tetrahydro-1H-(1)benzazepin-2-one in 5 steps.

L6 ANSWER 3 OF 11 REGISTRY COPYRIGHT 1997 ACS
RN 151258-03-6 REGISTRY
CN 1H-Azepine-1-acetic acid, 3-[[3-[[[2,3-bis(acetyloxy)propoxy]hydroxy phosphinyl]oxy]-1-oxo-2-[[(phenylmethoxy)carbonyl]amino]propyl]amino]hexahydro-2-oxo-, methyl ester, calcium salt (2:1), [3S-[3R*[R*(S*)]]]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C27 H38 N3 O14 P . 1/2 Ca
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



●1/2 Ca

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 120:8969 Amidic derivatives of (R)-glycerophosphoryl-(S)-serine or of its diacyl derivative, process for their preparation, and their pharmaceutical compositions for the improvement of learning processes. Moroni, Enzo (Magis Farmaceutici S.p.A., Italy). Eur. Pat. Appl. EP 557936 A1 930901, 35 pp. DESIGNATED STATES: R: BE, CH, DE, DK, ES, FR, GB, IT, LI, NL, PT. (English). CODEN: EPXXDW. APPLICATION: EP 93-102786 930223. PRIORITY: IT 92-MI437 920227.

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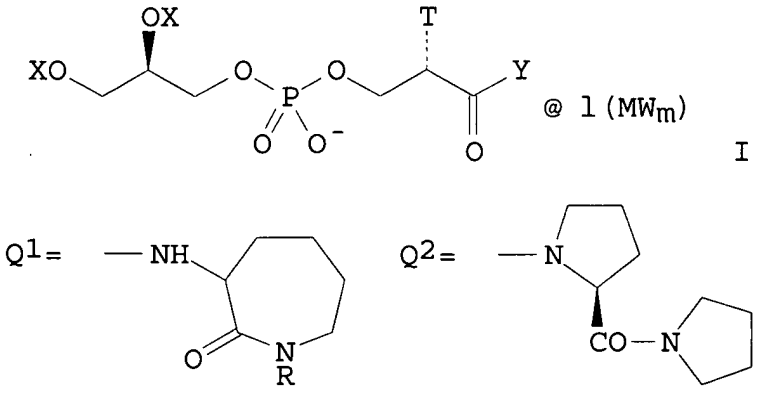


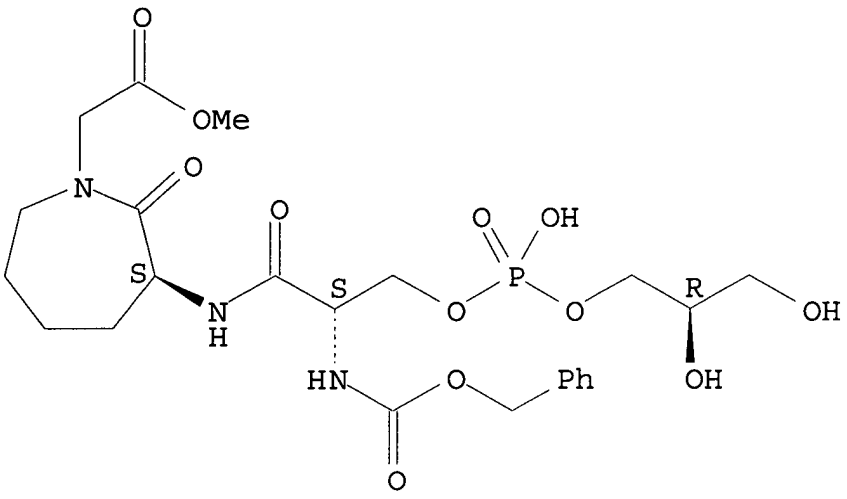
I

Searched By: Mary Hale 308-4258

AB Title compds. I [Y = Q1, Q2; R = H, CH2CO2Me, CH2CONH2, CH2CH2OH, CH2CHO; X = H, acyclic group (e.g., R'CO where R' = C1-20 alkyl with optional double bonds); T = NH2, NH3+; M = alk. earth metal; W = SO42-, Cl-, Br-, AcO-, tartrate; m = 0 (with T = NH2), or 1 or 2 (depending upon W); l = 0, 1/2 (provided that T = NH3+ when l = 0)] were prepd. as drugs for improvement of learning and memory processes. For example, (S)-(-)-.alpha.-amino-.epsilon.-caprolactam underwent protection of the amino group with benzyl chloroformate, N-alkylation of the ring N by NaH and BrCH2CO2Me, hydrogenolysis of the protecting group, and DCC-mediated amidation with N-(benzyloxycarbonyl)-(S)-serine to give (S)-HOCH2CH(NHCO2CH2Ph)CONHY [Y = (S)-Q1, R = CH2CO2Me (II). Condensation of POCl3 with (S)-isopropylideneglycerol and II, deprotection, and O-acetylation gave I [X = Ac, T = NH2, Y = (S)-Q1, R = CH2CO2Me, l = 1/2, M = Ca, m = 0] (III). In tests for reversal of scopolamine-induced amnesia in rats, III was more active i.p. than 3 ref. stds., including glycerolphosphorylserine and (S)-3-(formylamino)-.epsilon.-caprolactam.

L6 ANSWER 4 OF 11 REGISTRY COPYRIGHT 1997 ACS
RN 151258-02-5 REGISTRY
CN 1H-Azepine-1-acetic acid, 3-[[3-[[(2,3-dihydroxypropoxy)hydroxyphosphinyl]oxy]-1-oxo-2-[[(phenylmethoxy)carbonyl]amino]propyl]amino]hexahydro-2-oxo-, methyl ester, calcium salt (2:1), [3S-[3R*[R*(S*)]]]-(9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C23 H34 N3 O12 P . 1/2 Ca
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



●1/2 Ca

1 REFERENCES IN FILE CA (1967 TO DATE)
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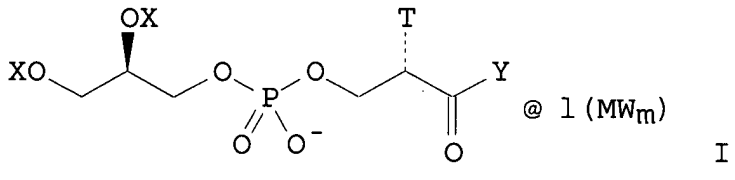

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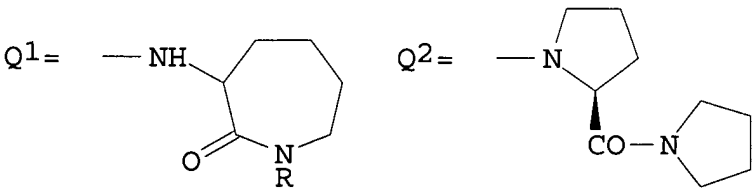

Searched By: Mary Hale 308-4258

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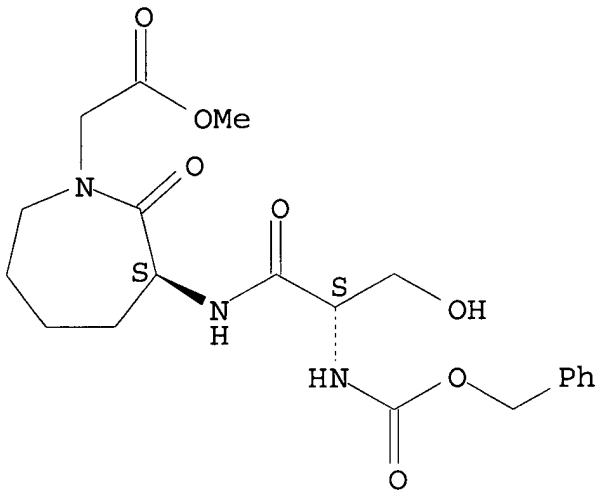
L6 ANSWER 5 OF 11 REGISTRY COPYRIGHT 1997 ACS
RN 151258-01-4 REGISTRY
CN 1H-Azepine-1-acetic acid, hexahydro-3-[[3-hydroxy-1-oxo-2-[[(phenylmethoxy)carbonyl]amino]propyl]amino]-2-oxo-, methyl ester, [S-(R*,R*)]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C20 H27 N3 O7
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



1 REFERENCES IN FILE CA (1967 TO DATE)
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REFERENCE 1: 120:8969 Amidic derivatives of (R)-glycerophosphoryl-(S)-serine or of its diacyl derivative, process for their preparation, and their pharmaceutical compositions for the improvement of learning processes. Moroni, Enzo (Magis Farmaceutici S.p.A., Italy). Eur. Pat. Appl. EP 557936 A1 930901, 35 pp. DESIGNATED STATES: R: BE, CH, DE, DK, ES, FR, GB, IT, LI, NL, PT. (English). CODEN: EPXXDW. APPLICATION: EP 93-102786 930223. PRIORITY: IT 92-MI437 920227.

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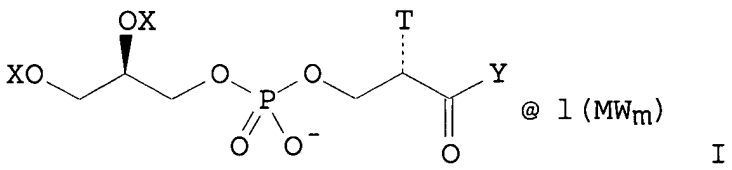

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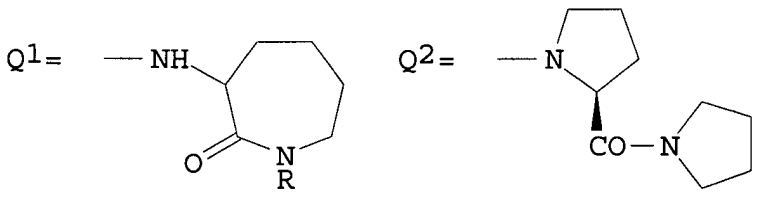

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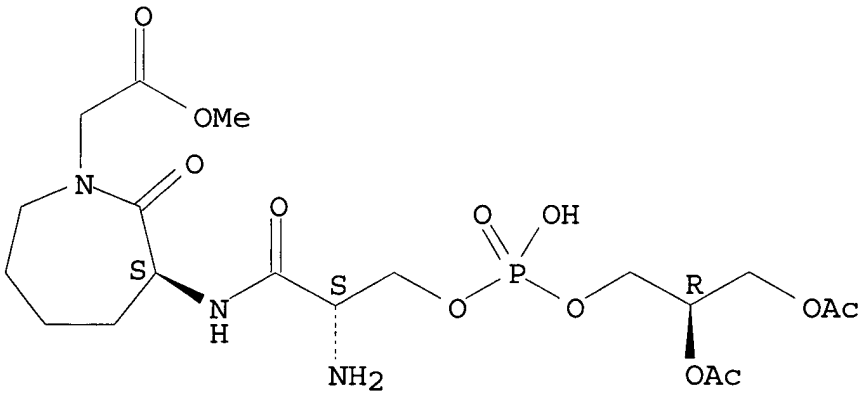
optional double bonds); T = NH2, NH3+; M = alk. earth metal; W = SO42-, Cl-, Br-, AcO-, tartrate; m = 0 (with T = NH2), or 1 or 2 (depending upon W); l = 0, 1/2 (provided that T = NH3+ when l = 0)] were prepd. as drugs for improvement of learning and memory processes. For example, (S)-(-)-.alpha.-amino-.epsilon.-caprolactam underwent protection of the amino group with benzyl chloroformate, N-alkylation of the ring N by NaH and BrCH2CO2Me, hydrogenolysis of the protecting group, and DCC-mediated amidation with N-(benzyloxycarbonyl)-(S)-serine to give (S)-HOCH2CH(NHCO2CH2Ph)CONHY [Y = (S)-Q1, R = CH2CO2Me (II). Condensation of POCl3 with (S)-isopropylideneglycerol and II, deprotection, and O-acetylation gave I [X = Ac, T = NH2, Y = (S)-Q1, R = CH2CO2Me, l = 1/2, M = Ca, m = 0] (III). In tests for reversal of scopolamine-induced amnesia in rats, III was more active i.p. than 3 ref. stds., including glycerolphosphorylserine and (S)-3-(formylamino)-.epsilon.-caprolactam.

L6 ANSWER 6 OF 11 REGISTRY COPYRIGHT 1997 ACS
RN 151257-92-0 REGISTRY
CN 1H-Azepine-1-acetic acid, 3-[[2-amino-3-[[[2,3-bis(acetyloxy)propoxy]hydroxyphosphinyl]oxy]-1-oxopropyl]amino]hexahydro-2-oxo-, methyl ester, calcium salt (2:1), [3S-[3R*[R*(S*)]]]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C19 H32 N3 O12 P . 1/2 Ca
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



1/2 Ca

Searched By: Mary Hale 308-4258

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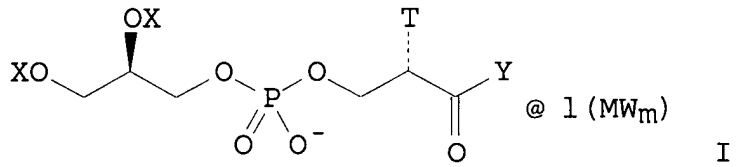

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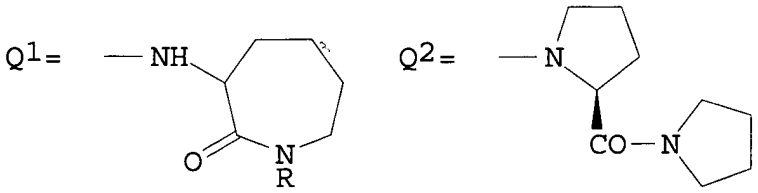
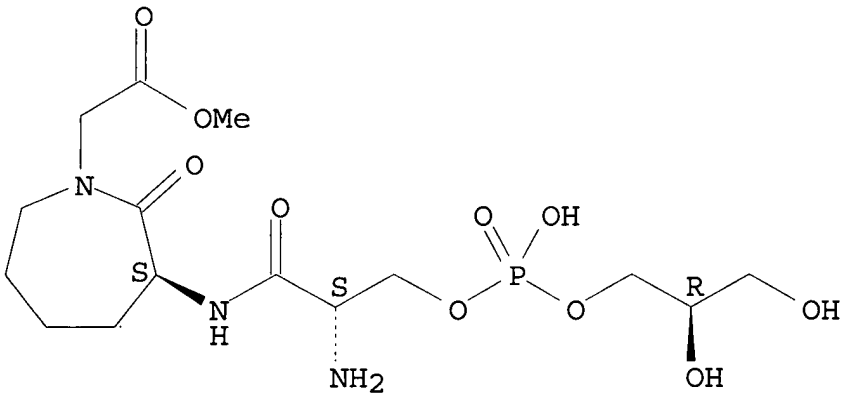


AB Title compds. I [Y = Q1, Q2; R = H, CH2CO2Me, CH2CONH2, CH2CH2OH, CH2CHO; X = H, acyclic group (e.g., R'CO where R' = C1-20 alkyl with optional double bonds); T = NH2, NH3+; M = alk. earth metal; W = SO42-, Cl-, Br-, AcO-, tartrate; m = 0 (with T = NH2), or 1 or 2 (depending upon W); l = 0, 1/2 (provided that T = NH3+ when l = 0)] were prepd. as drugs for improvement of learning and memory processes. For example, (S)-(-)-.alpha.-amino-.epsilon.-caprolactam underwent protection of the amino group with benzyl chloroformate, N-alkylation of the ring N by NaH and BrCH2CO2Me, hydrogenolysis of the protecting group, and DCC-mediated amidation with N-(benzyloxycarbonyl)-(S)-serine to give (S)-HOCH2CH(NHCO2CH2Ph)CONHY [Y = (S)-Q1, R = CH2CO2Me (II). Condensation of POCl3 with (S)-isopropylideneglycerol and II, deprotection, and O-acetylation gave I [X = Ac, T = NH2, Y = (S)-Q1, R = CH2CO2Me, l = 1/2, M = Ca, m = 0] (III). In tests for reversal of scopolamine-induced amnesia in rats, III was more active i.p. than 3 ref. stds., including glycerolphosphorylserine and

(S)-3-(formylamino)-.epsilon.-caprolactam.

L6 ANSWER 7 OF 11 REGISTRY COPYRIGHT 1997 ACS
RN 151257-91-9 REGISTRY
CN 1H-Azepine-1-acetic acid, 3-[[2-amino-3-[[(2,3-dihydroxypropoxy)hydroxyphosphinyl]oxy]-1-oxopropyl]amino]hexahydro-2-oxo-, methyl ester, calcium salt (2:1), [3S-[3R*[R*(S*)]]]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C15 H28 N3 O10 P . 1/2 Ca
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

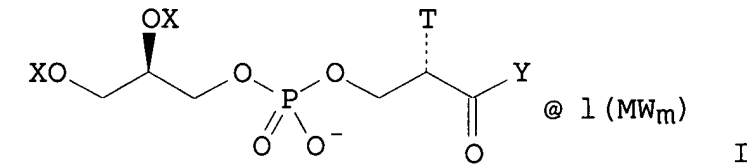


●1/2 Ca

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 120:8969 Amidic derivatives of (R)-glycerophosphoryl-(S)-serine or of its diacyl derivative, process for their preparation, and their pharmaceutical compositions for the improvement of learning processes. Moroni, Enzo (Magis Farmaceutici S.p.A., Italy). Eur. Pat. Appl. EP 557936 A1 930901, 35 pp. DESIGNATED STATES: R: BE, CH, DE, DK, ES, FR, GB, IT, LI, NL, PT. (English). CODEN: EPXXDW. APPLICATION: EP 93-102786 930223. PRIORITY: IT 92-MI437 920227.

GI



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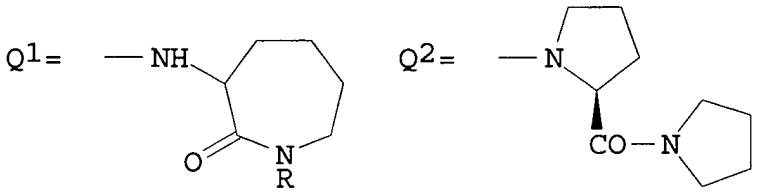
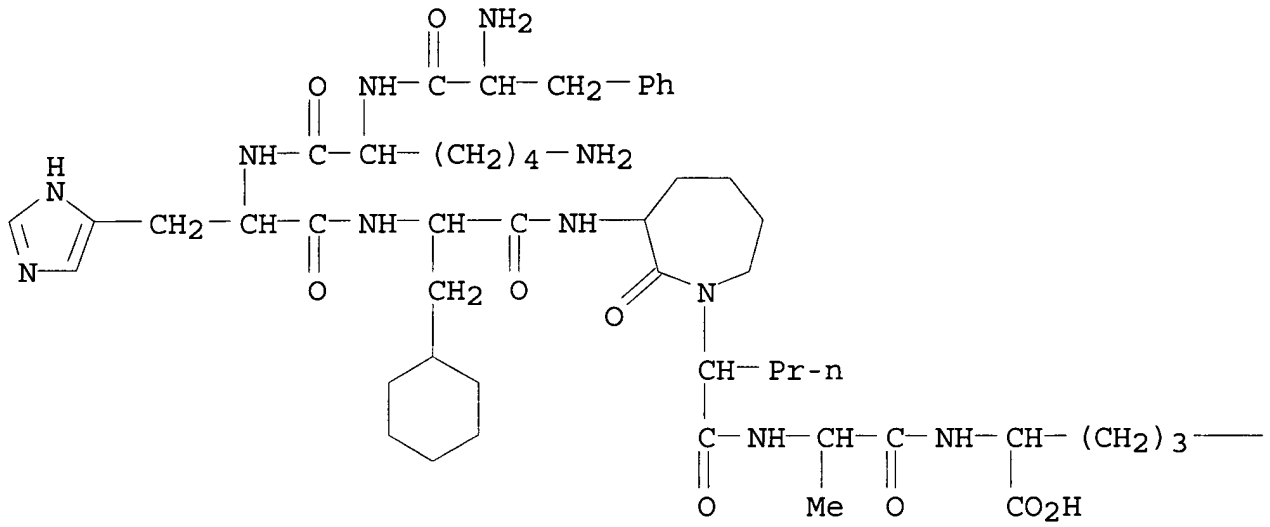


AB Title compds. I [Y = Q1, Q2; R = H, CH2CO2Me, CH2CONH2, CH2CH2OH, CH2CHO; X = H, acyclic group (e.g., R'CO where R' = C1-20 alkyl with optional double bonds); T = NH2, NH3+; M = alk. earth metal; W = SO42-, Cl-, Br-, AcO-, tartrate; m = 0 (with T = NH2), or 1 or 2 (depending upon W); l = 0, 1/2 (provided that T = NH3+ when l = 0)] were prepd. as drugs for improvement of learning and memory processes. For example, (S)-(-)-.alpha.-amino-.epsilon.-caprolactam underwent protection of the amino group with benzyl chloroformate, N-alkylation of the ring N by NaH and BrCH2CO2Me, hydrogenolysis of the protecting group, and DCC-mediated amidation with N-(benzyloxycarbonyl)-(S)-serine to give (S)-HOCH2CH(NHCO2CH2Ph)CONHY [Y = (S)-Q1, R = CH2CO2Me (II). Condensation of POCl3 with (S)-isopropylideneglycerol and II, deprotection, and O-acetylation gave I [X = Ac, T = NH2, Y = (S)-Q1, R = CH2CO2Me, l = 1/2, M = Ca, m = 0] (III). In tests for reversal of scopolamine-induced amnesia in rats, III was more active i.p. than 3 ref. stds., including glycerolphosphorylserine and (S)-3-(formylamino)-.epsilon.-caprolactam.

L6 ANSWER 8 OF 11 REGISTRY COPYRIGHT 1997 ACS
RN 133319-78-5 REGISTRY
CN L-Arginine, N2-[N-[2-[3-[[3-cyclohexyl-N-[N-(N2-L-phenylalanyl-L-lysyl)-L-histidyl]-L-alanyl]amino]hexahydro-2-oxo-1H-azepin-1-yl]-1-oxopentyl]-D-alanyl]-, [S-(R*,R*)]- (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE
MF C50 H80 N14 O9
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

PAGE 1-A



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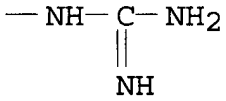


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 114:221389 Preparation of anaphylatoxin-receptor peptide ligands for modulating anaphylatoxic activity and treatment of inflammation. Kawai, Megumi; Or, Yat Sun; Wiedeman, Paul E.; Luly, Jay R.; Moyer, Mikel P. (Abbott Laboratories, USA). PCT Int. Appl.

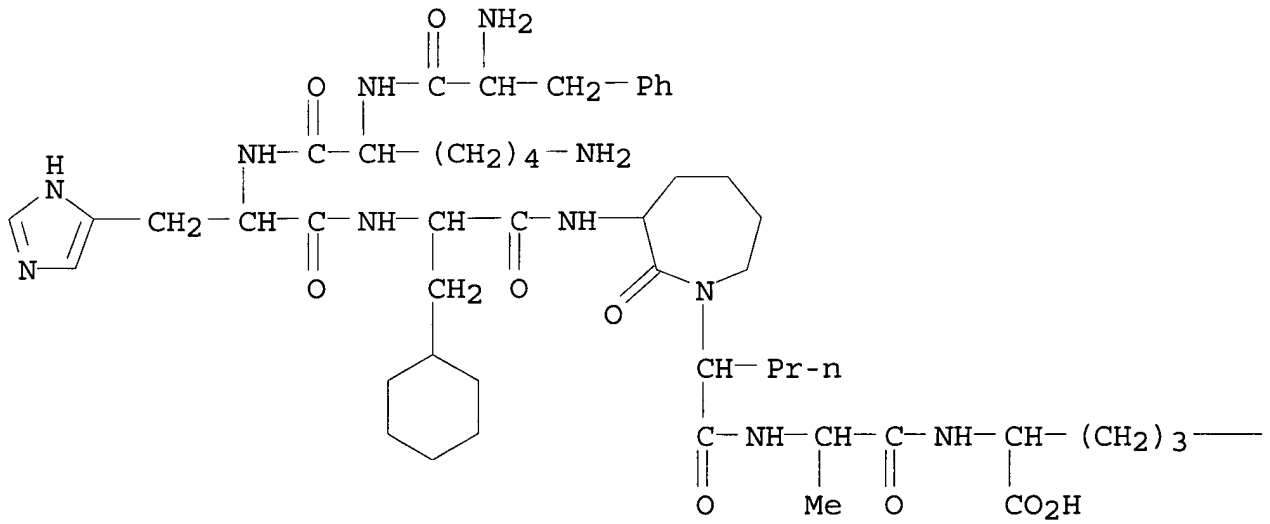
Searched By: Mary Hale 308-4258

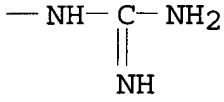
WO 9009162 A2 900823, 165 pp. DESIGNATED STATES: W: CA, JP, US; RW: AT, BE, CH, DE, DK, ES, FR, GB, IT, LU, NL, SE. (English). CODEN: PIXXD2. APPLICATION: WO 90-US296 900116. PRIORITY: US 89-304693 890131.

AB Oligopeptides and oligopeptide analogs are prepd. as ligands for the anaphylatoxin receptor and are useful in the treatment of inflammatory disease states and modulation of anaphylatoxin activity. Thus, H-Phe-Lys-Ala-[(2S)-2-amino-3-cyclohexylpropanoyl]-[(2S-2-amino-3-cyclohexylpropanoyl]-Leu-D-Ala-Arg-OH (prepn. given) had a Ki (inhibition const.) of 0.098 .mu.M for anaphylatoxin receptor binding. The invention discloses >400 peptides.

L6 ANSWER 9 OF 11 REGISTRY COPYRIGHT 1997 ACS
RN 133215-61-9 REGISTRY
CN L-Arginine, N2-[N-[2-[3-[[3-cyclohexyl-N-[N-(N2-L-phenylalanyl-L-lysyl)-L-histidyl]-L-alanyl]amino]hexahydro-2-oxo-1H-azepin-1-yl]-1-oxopentyl]-D-alanyl]-, [R-(R*,S*)]- (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE
MF C50 H80 N14 O9
SR CA
LC STN Files: CA, CAPLUS, TOXLIT, USPATFULL

PAGE 1-A





1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 114:221389 Preparation of anaphylatoxin-receptor peptide ligands for modulating anaphylatoxic activity and treatment of inflammation. Kawai, Megumi; Or, Yat Sun; Wiedeman, Paul E.; Luly, Jay R.; Moyer, Mikel P. (Abbott Laboratories, USA). PCT Int. Appl. WO 9009162 A2 900823, 165 pp. DESIGNATED STATES: W: CA, JP, US; RW: AT, BE, CH, DE, DK, ES, FR, GB, IT, LU, NL, SE. (English). CODEN: PIXXD2. APPLICATION: WO 90-US296 900116. PRIORITY: US 89-304693 890131.

AB Oligopeptides and oligopeptide analogs are prepd. as ligands for the anaphylatoxin receptor and are useful in the treatment of inflammatory disease states and modulation of anaphylatoxin activity. Thus, H-Phe-Lys-Ala-[(2S)-2-amino-3-cyclohexylpropanoyl]-[(2S-2-amino-3-cyclohexylpropanoyl]-Leu-D-Ala-Arg-OH (prepn. given) had a Ki (inhibition const.) of 0.098 .mu.M for anaphylatoxin receptor binding. The invention discloses >400 peptides.

L6 ANSWER 10 OF 11 REGISTRY COPYRIGHT 1997 ACS
RN 78444-88-9 REGISTRY
CN L-Methioninamide, N-[[3-[[2-amino-3-(4-hydroxyphenyl)-1-oxopropyl]amino]hexahydro-2-oxo-1H-azepin-1-yl]acetyl]-L-phenylalanyl-, [R-(R*,S*)]- (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE
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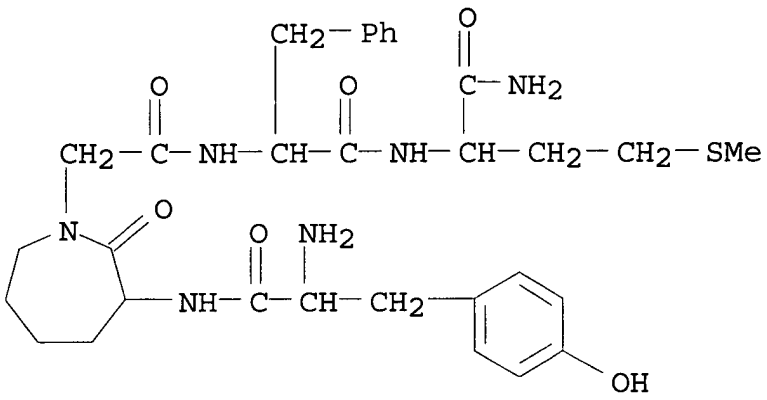
LC STN Files: CA, CAPLUS, USPATFULL

Searched By: Mary Hale 308-4258



2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 97:92729 Computer graphics and chemical synthesis in the study of conformation of biologically active peptides. Freidinger, R. M. (Res. Lab., Merck Sharp Dohme, West Point, PA, 19486, USA). Pept.: Synth., Struct., Funct., Proc. Am. Pept. Symp., 7th, 673-83. Editor(s): Rich, Daniel H.; Gross, Erhard. Pierce Chem. Co.: Rockford, Ill. (English) 1981. CODEN: 47LMAO.

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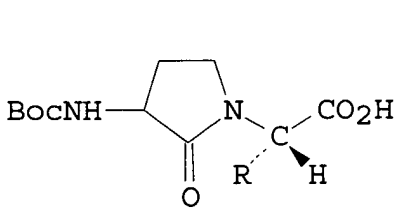

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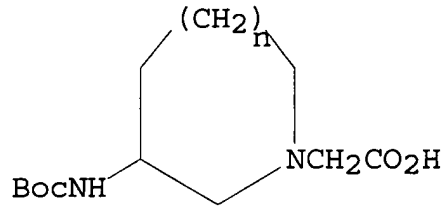

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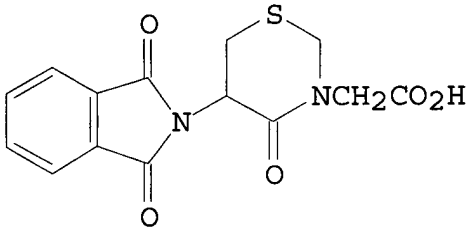
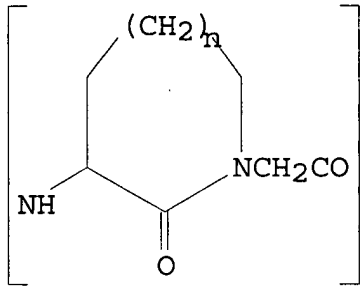


III

cyclo



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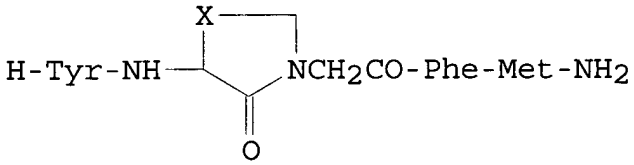

V

AB Interactive computer graphics and chem. synthesis were used as complementary tools for the study of peptide conformation; the Merk Mol. Modeling System was applied to the display of structures and the study of their 3-dimensional properties. Computer modeling was used for a comparison of Types I and II' .beta.-turn conformations of Ac-Ala-Ala-NHMe. The use of .gamma.-, .delta.-, and .epsilon.-lactams were studied, and synthetic routes to lactams I (Boc = Me3CO2C; R = H, CH2CHMe2), II (n = 1, 2), and III were devised. Computer superposition illustrated a good correspondence between the backbones of the proposed LH-releasing hormone .beta.-turn and the .beta.-lactam. Computer modeling was applied to cyclic hexapeptide lactams IV (n = 0, 1, 2). Enkephalin lactam analogs V [X = CH2, CH2CH2, CH2S, lactam configuration = D and L; X = (CH2)3, lactam configuration = D] were prepd., and their biol. activities were dependent on lactam configuration and ring size.

REFERENCE 2: 95:81532 Long-lasting agonists of enkephalin. Veber, Daniel F.; Freidinger, Roger M. (Merck and Co., Inc., USA). U.S. US 4254107 810303, 11 pp. (English). CODEN: USXXAM. APPLICATION: US 79-97758 791127.

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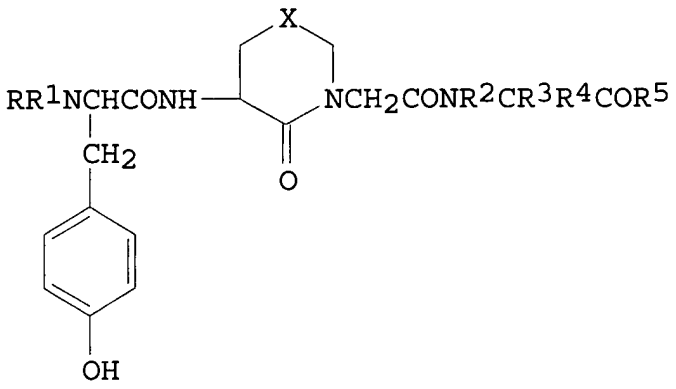

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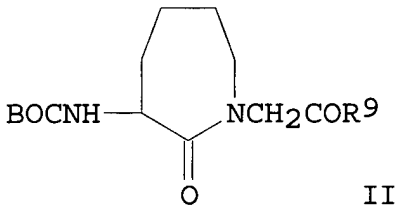

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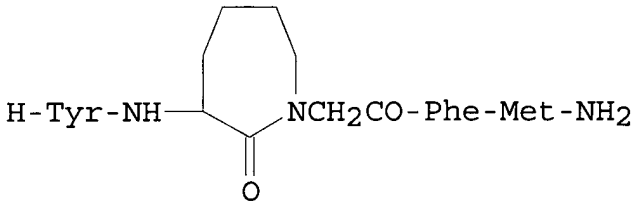

III

AB Peptides I [R = H, C1-6 alkyl, H-Arg, H-Lys-Arg; R1 = H, C1-6 alkyl, alkyl, cyclopropylmethyl; R2 = H, Me; R3 = (un)substituted benzyl, iodolylmethyll, imidazolylmethyl, CH2CHMe2; R4 = H, Me; R3R4 = CHPh; R5 = OR6 (R6 = H, C1-6 alkyl, cation), NR7R8 (R7 and R8 = H, C1-6 alkyl, CH2CH2NMe2, CH2CH2N(O)Me2), Met-OH, Met-NH2, methioninol (Met-ol), D-Met-NH2, MeMet-NH2, Met(O)-NH2, Met(O)-ol, Leu-NH2, MeLeu-NH2, D-Leu-NH2, Pro-NH2; X = S, (CH2)n (n = 0, 1, 2)], having long-lasting enkephalin agonist activity, were prepd. as analgesics and agents for treating schizophrenia. Thus, BOC-(R)-Lys(CO2CH2C6H4Cl-2)-OMe (BOC = Me3CO2C) underwent hydrogenolysis and then reductive alkylation with glyoxylic acid to give BOC-(R)-Lys(CH2CO2H)-OMe, which was cyclized to give azepine II (R9 = OH). The latter was used in the solid-phase synthesis of II (R9 = Phe-Met-NH2), which was BOC-deblocked and then coupled to BOC-Tyr-ONSu (NSu = succinimido) to give the protected peptide amide, which was BOC-deblocked to give peptide III.

L6 ANSWER 11 OF 11 REGISTRY COPYRIGHT 1997 ACS
RN 78444-87-8 REGISTRY
CN L-Methioninamide, N-[[3-[[2-[[(1,1-dimethylethoxy)carbonyl]amino]-3-(4-hydroxyphenyl)-1-oxopropyl]amino]hexahydro-2-oxo-1H-azepin-1-yl]acetyl]-L-phenylalanyl-, [R-(R*,S*)]- (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE

Searched By: Mary Hale 308-4258

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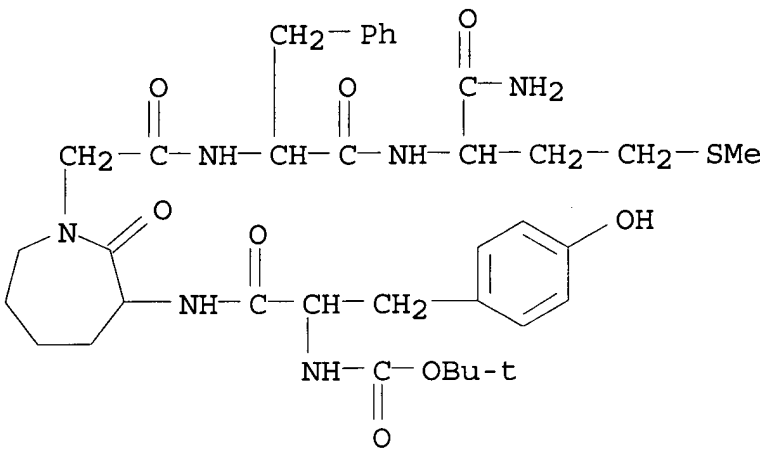
LC STN Files: CA, CAPLUS, USPATFULL



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

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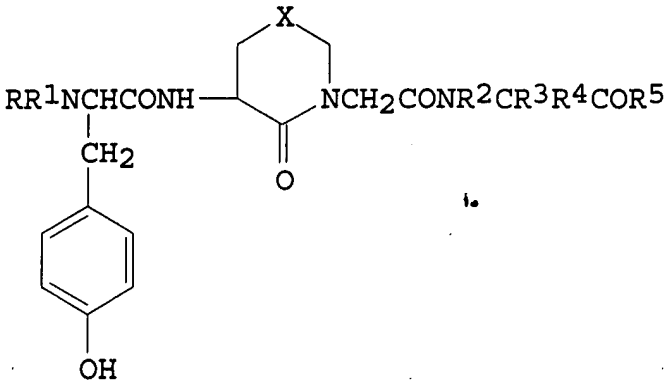
GI



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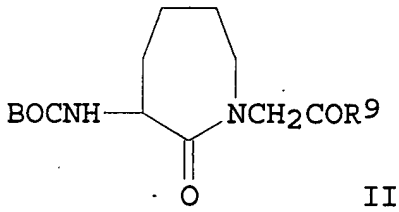

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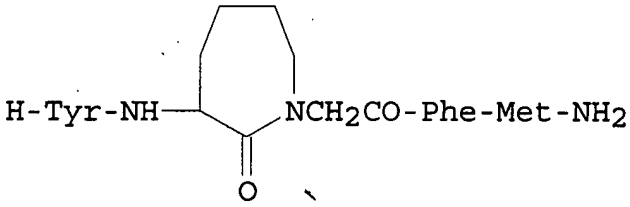

III

AB Peptides I [R = H, C1-6 alkyl, H-Arg, H-Lys-Arg; R1 = H, C1-6 alkyl, alkyl, cyclopropylmethyl; R2 = H, Me; R3 = (un)substituted benzyl, iodolylmethyll, imidazolylmethyl, CH2CHMe2; R4 = H, Me; R3R4 = CHPh; R5 = OR6 (R6 = H, C1-6 alkyl, cation), NR7R8 (R7 and R8 = H, C1-6 alkyl, CH2CH2NMe2, CH2CH2N(O)Me2), Met-OH, Met-NH2, methioninol (Met-ol), D-Met-NH2, MeMet-NH2, Met(O)-NH2, Met(O)-ol, Leu-NH2, MeLeu-NH2, D-Leu-NH2, Pro-NH2; X = S, (CH2)n (n = 0, 1, 2)], having long-lasting enkephalin agonist activity, were prepd. as analgesics and agents for treating schizophrenia. Thus, BOC-(R)-Lys(CO2CH2C6H4Cl-2)-OMe (BOC = Me3CO2C) underwent hydrogenolysis and then reductive alkylation with glyoxylic acid to give BOC-(R)-Lys(CH2CO2H)-OMe, which was cyclized to give azepine II (R9 = OH). The latter was used in the solid-phase synthesis of II (R9 = Phe-Met-NH2), which was BOC-deblocked and then coupled to BOC-Tyr-ONSu (NSu = succinimido) to give the protected peptide amide, which was BOC-deblocked to give peptide III.

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